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EXAMINER

FLOOD, MICHELE C

ART UNIT PAPER NUMBER

1654

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/668,601

Applicant(s)

SHAISH ET AL.

Examiner

Michele Flood

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 October 2004.
2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-18 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on October 4, 2004. Further acknowledgment is made of the receipt and entry of the declarations of Ami Ben-Amotz and Aviv Shaish filed under Rule 132 on October 4, 2004

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 102

Claim 1 as amended and Claims 8-10 is/are remain rejected under 35 U.S.C. 102(b) as being anticipated by Levy et al. (U). Applicant's arguments have been fully considered; however, the rejection stands for the reasons set forth in the previous Office and for the reasons set forth below.

Applicant claims a method for treating a disease selected from diabetes mellitus and atherosclerosis comprising administering to a subject an effective amount of crude *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans and 9-cis β -carotene.

Applicant's main argument is directed to the idea that the method of treatment taught by Levy does not encompass the limitation of newly amended Claim 1 comprising "the use of *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans and 9-cis β -carotene". However, Applicant's argument is not found persuasive

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because on page 55, Column 2, under “*Supplements*”, Levy clearly teaches the use of an encapsulated *Dunaliella* powder comprising the claim-designated ratio of ingredients. For example, Levy expressly teaches, “The β -carotene was comprised of two major isomers: all-trans (42%) and 9-cis (43%), [citation omitted]”. Moreover, Levy teaches a method of treating patients suffering from diabetes mellitus and at high risk of developing atherosclerosis comprising administering an effective amount of an extract obtained from *Dunaliella bardawil* in encapsulated form. Levy teaches that the administration of the algal extract inhibited the oxidation of LDL derived from diabetic patients.

The reference anticipates the claimed subject matter.

Claim 1 as amended and Claims 2, 8-9, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoko et al. (V). Newly applied as necessitated by amendment.

Yoko teaches a method for reducing triglycerides in the plasma of a subject comprising administering an effective amount of *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans β -carotene and 9-cis β -carotene to patients with hyperlipidemia. Yoko teaches, “The plasma level of total cholesterol (TC), triglyceride (TG), LDL-cholesterol (LDL), lipid peroxide (LPO) and total lipid (T-Lip) significantly decreased by the administration of *Dunaliella* powder.” Yoko further teaches that *Dunaliella* powder is useful material of functional healthy food not only for hyperlipidemia, but also arteriosclerosis because the level of LPO was decreased in

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hyperlipidemic patients. Hence, Yoko also teaches a method for treating atherosclerosis.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claim 1 as amended and Claims 2, 8-10, 16 and 17 is/are remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (U) and Levy et al. (W), and further in view of Yoko et al. (V). Newly applied as necessitated by amendment.

The rejection stands for the reasons set forth in the previous Office action, the reasons set forth above, and for the reasons set forth below.

Applicant's arguments and the declaration of Ami Ben-Amotz filed under Rule 132 have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary reference of Levy was relied upon because Levy (U) teaches orally administering 60 mg/day of a beta-carotene containing extract of *Dunaliella bardawil* to diabetic patients

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affected a significant reduction in LDL susceptibility to oxidation, as exhibited by increased lag time and reduction in malondialdehyde (MDA) and lipid peroxides (PD). As set forth above, Levy teaches a method of treating diabetes mellitus comprising administering to a diabetic subject an effective amount of crude *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans and 9-cis β -carotene. Because Levy does not expressly teach a method of treating a disease wherein the disease is atherosclerosis, the secondary reference of Levy (W) was relied upon because at the time the invention was made it was well known in the art of medicine that atherogenesis involves oxidative modification of low-density lipoprotein and that accelerated atherosclerosis is common in patients with diabetes mellitus, as evidenced by the teachings of Levy (U); and, that atherogenesis involves oxidative modification of low-density lipoprotein (LDL), as evidenced by the teachings of Levy (W). For instance, Levy (W) teaches a method for reducing the susceptibility of LDL to lipid peroxidation comprising orally administering an effective amount of an extract derived from *Dunaliella bardawil* to healthy patients. Furthermore, Levy (W) teaches that ingestion of a stereoisomeric mixture of 9-cis and all-trans beta-carotene derived from the alga *Dunaliella bardawil* caused a 1.8-fold carotene elevation in plasma and that oxidation modification of LDL, measured for both dosage intakes, was reduced.

In view of the Ben-Amotz' declaration, Applicant argues that one of ordinary skill in the art would not have looked to either of the teachings of Levy (U or W) because both of the aforementioned cited references are based on the hypothesis that "atherogenesis involves oxidative modification of LDL, which is associated with the

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depletion of the LDL endogenous anti-oxidants", and the "enrichment of LDL with the anti-oxidant β -carotene has the potential of reducing the susceptibility of LDL to lipid peroxidation" (Levy (W), abstract). Applicant further argues, "In other words, LDL is protected against oxidation by anti-oxidants, and the β -carotene contained in *Dunaliella* acts as an anti-oxidant (Levy (W), pg. 13, last paragraph)." Finally, Applicant further argues, "However, in recent years, and certainly by the filing date of the application, this hypothesis had been proven to be in error." Then, Applicant refers to the declaration of Ami Ben-Amotz filed under Rule 132, as well as a number of articles, in an attempt to provide support and reproof of the hypothesis relied upon in the articles of Levy. The Office respectfully deems that neither Applicant's arguments nor the articles relied upon in the Ben-Amotz' declaration are persuasive or commensurate in scope to the limitations of the instantly claimed invention. Firstly, with regard to paragraph number 8 of the Ben-Amotz' declaration, the declaration refers to the references of Yusuf et al. [Annex B, 2000] and Hegele. R. A. [Annex C, 2000], wherein the articles describe observational and experimental studies directed to the oral administration of various antioxidants and vitamins in the treatment of coronary heart disease, atherosclerosis, degenerative vascular diseases, cancer or diabetes. For example, Yusuf [Annex B] discloses the oral administration of a high dose of Vitamin E to patients suffering from either cardiovascular disease or diabetes who were at high risk for cardiovascular events, wherein Yusuf concludes that Vitamin E did not reduce the incidence of cardiovascular events. The Office notes that on page 154, Column 1, lines 1-4, Yusuf clearly teaches, "Oxidative modification of low-density lipoprotein is an important step in

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the development and progression of atherosclerosis in experimental studies [citation omitted].” Like, Yusuf, Hegele discloses the administration of Vitamin E to cardiovascular high-risk patients and diabetic patients, wherein Hegele concludes that treatment with Vitamin E 400 IU/day had no apparent influence of cardiovascular outcomes. However, nowhere in the references of either Yusuf or Hegele is there a disclosure or suggestion for the administration of the claim-designated composition for the treatment of any of the claim-designated disease conditions. In other words, Applicant has relied upon nonanalogous art; the prior art references are not reasonably pertinent to the particular problem with which the Applicant is concerned. Finally, on page 15 of Applicant's “REMARKS”, lines 4-6, Applicant refers to an annex A; however, no annex A was found in the declaration filed by Ben-Amotz.

Secondly, with regard to paragraph number 9 of the Ben-Amotz' declaration, the declaration refers to the reference of Kritharides, L. et al. [Annex D, 2002], wherein Kritharides reviews the use of various antioxidant supplements in the prevention of coronary heart disease (CHD). Applicant rightfully argues that Kritharides concludes that “supplements of α -tocopherol and β -carotene cannot be recommended for the treatment or prevention of CHD (abstract).” However, nowhere in the reference of Kritharides is there a disclosure or suggestion for the administration of the claim-designated composition for the treatment of any of the claim-designated disease conditions. In other words, Applicant has relied upon nonanalogous art; the prior art reference is not reasonably pertinent to the particular problem with which the Applicant is concerned. Finally, the Office notes that Kritharides expressly teaches, in the first line

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of the abstract, "There is clear evidence of lipoprotein oxidation in atherosclerotic lesions."

Thirdly, with regard to paragraph number 10 of the Ben-Amotz' declaration, the declaration refers to the reference of Zureik, M. et al. [Annex E, 2004], wherein Zureik describes the results of a study carried out to determine the effects of long-term daily low-dose administration of antioxidant vitamins, including β -carotene, and minerals to healthy subjects. In the abstract, Zureik concludes that "no beneficial effects of long-term daily low-dose supplementation of antioxidant vitamins and minerals on carotid atherosclerosis and arterial stiffness." While it appears that Applicant asserts that the results of the Zureik' study would lead one of ordinary skill in the art to disregard the teachings of Levy because Zureik alleges that antioxidant supplementation has no beneficial effect in the treatment of atherosclerosis, again the Office notes that nowhere in the reference of Zureik is there a disclosure or suggestion for the administration of the claim-designated composition for the treatment of any of the claim-designated disease conditions. Applicant has repeatedly relied upon articles that are not analogous to the limitations of the claimed invention. Moreover, Zureik expressly teaches on page 1485, Column 1, lines 1-9, "The results of several animal experimental and population-based epidemiological studies have suggested that enhanced lipid peroxidation is associated with atherogenesis and cardiovascular diseases [citation omitted]. Many observational studies show that a high dietary intake of high blood concentration of antioxidant vitamins is associated with reduce risk of cardiovascular diseases [citation omitted]. Dietary antioxidants are recognized to protect against lipid peroxidation." Thus, contrary

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to Applicant's arguments and the declaration of Ben-Amotz, at the time the invention was made and at the date of the filing of the instant application, one of ordinary skill in the art would have indeed looked to and not disregarded either Levy (U) or Levy (W) in the making of the instantly claimed method for treating atherosclerosis because Levy (U) and Levy (W) render the claimed invention obvious absent evidence to the contrary, since the state of the art at the time the invention was made and thereafter clearly recognized a nexus between dietary antioxidant supplementation for its beneficial effect to protect against lipid peroxidation and the association of enhanced lipid peroxidation in the development of atherogenesis and cardiovascular diseases, as evidenced by references relied upon in the Ben-Amotz' declaration to disprove the basis of the hypothesis set forth in the Levy (U and W) references that "atherogenesis involves oxidative modification of LDL, which is associated with the depletion of the LDL endogenous anti-oxidants", and the "enrichment of LDL with the anti-oxidant β -carotene has the potential of reducing the susceptibility of LDL to lipid peroxidation" (Levy (W), abstract).

Thus, with Levy (U) teaching a method for treating diabetes mellitus comprising administering to a subject in need thereof an effective amount of encapsulated crude *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans and 9-cis β -carotene, and with Levy (W) suggesting, "Supplementation of beta-carotene may be an important approach to reducing atherosclerosis via its inhibitory effect on the formation of atherogenic oxidized LDL" comprising an effective amount of isomers of β -carotene from *Dunaliella*, it would have been obvious to one of ordinary skill in the art to use the

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method for treating diabetes taught by Levy (U) to provide a method for treating atherosclerosis because Levy (U) teaches, "Increased susceptibility to oxidation of LDL derived from patients with diabetes mellitus is associated with abnormal LDL lipid composition and antioxidant content. Natural beta-carotene dietary supplementation normalizes the enhanced LDL oxidation and consequently may be of importance in delaying accelerated development of atherosclerosis in these patients." Furthermore, on page 58, Column 1, line 43 to Column 2, line 2, Levy (U) discloses that diabetic LDL lipid composition is characterized by an increase in cholesterol, decrease in phospholipid and redistribution of LDL phospholipids, wherein in those alterations lead necessarily to modification in LDL fluidity and to an overall shift in LDL mobility, receptor binding and atherogenicity; and, on page 58, Column 2, lines 20-22, Levy expressly teaches, "We have exhibited a protective effect of β -carotene against oxidation upon a three-week dietary supplementation in diabetic patients." Thus, as each of Levy (U) and Lévy (W) teach that the oral administration of effective amounts of an extract derived from *Dunaliella bardawil* to either a diabetic patient or a healthy patient have the beneficial functional inhibitory effect on the susceptibility of LDL to oxidative modification, one of ordinary skill in the art would have been further motivated and one would have had a reasonable expectation of success to modify the referenced methods by adjusting the dose amounts of the referenced extracts to provide a method for treating atherosclerosis because Levy (U) teaches that dietary supplementation of a natural isomer mixture of beta-carotene derived from an extract of *Dunaliella bardawil* delays oxidation of LDL derived from patients with mellitus; and, Levy (W) similarly

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teaches that dietary supplementation of the same algal extract taught by Levy (U) delays oxidation of LDL in healthy patients and "Atherogenesis involves oxidative modification of low-density lipoprotein (LDL), which is associated with the depletion of the LDL endogenous oxidants." At the time the invention was made, it also would have been obvious to one of ordinary skill in the art and one would have been highly motivated and had a reasonable expectation of success to use the method of treating diabetic patients taught by Levy (U) to provide the instantly claimed method for treating atherosclerosis because, as set forth above, Yoko also taught a method for reducing triglycerides in the plasma of a subject comprising administering an effective amount of *Dunaliella* powder comprising an approximately 1:1 ratio of all-trans β -carotene and 9-cis β -carotene to patients with hyperlipidemia. Yoko teaches, "The plasma level of total cholesterol (TC), triglyceride (TG), LDL-cholesterol (LDL), lipid peroxide (LPO) and total lipid (T-Lip) significantly decreased by the administration of *Dunaliella* powder." Yoko further teaches that *Dunaliella* powder is useful not only for hyperlipidemia, but also arteriosclerosis because the level of LPO was decreased in hyperlipidemic patients.

As each of the references indicate that the various proportions and amounts of the ingredients used in the claimed method of treatments are result variables, they would have been routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

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Claim 1 as amended and Claims 3-10 is/are remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (U) in view of Beck (A), Pan et al. (B), Heyman et al. (D) and Smith (N). The rejection stands for the reasons set forth in the previous Office action, the reasons set forth above, and for the reasons set forth below.

Applicant's arguments and the declaration of Avish Shaish filed under Rule 132 have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

Applicant traverses the rejection set forth in the previous Office action based on the idea that one of ordinary skill would disregard the Levy' reference for the same reasons set forth above in Applicant's arguments.

In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary reference of Levy (U) was relied upon for the reasons set forth in the previous Office action and for the reason set forth immediately above. Because Levy taught the claimed method for treating diabetes mellitus except for the instantly claimed ingredients, the secondary references of Beck, Pan, Heyman and Smith were relied upon because Beck taught a method for the treatment of normolipidaemic diabetes

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mellitus comprising orally administering an effective amount of bezafibrate; Pan taught a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an antihyperlipoproteinemic agent, e.g., fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate in combination with a cholesterol lowering drug, ACE inhibitor, in Column 9, lines 32-58 and Pan taught administering gemfibrozil capsules either alone in combination with a cholesterol lowering drug, ACE inhibitor in the treatment of diabetes mellitus; Heyman taught a method of treating diabetes mellitus comprising administering an effective amount of a thiazolidinedione, e.g., troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject; and, Smith taught a method of treating diabetes mellitus comprising administering rosiglitazone.

With regard to the declaration of Shaish filed under Rule 132, wherein Shaish provides experimental results showing that the combination of *Dunaliella* powder together with a PPAR γ (i.e., rosiglitazone) shows an unexpected improvement in the treatment of diabetes as opposed to the results with either component alone, the Office deems that the Shaish' disclosure is not commensurate in scope to the limitations of the claimed invention as the claimed invention is directed to a method for treating diabetes mellitus comprising administering to a subject an effective amount of the claim-designated ingredient together with one or more activators of nuclear receptors vs. a method for improving treating diabetes mellitus comprising administering to a subject an effective amount of crude *Dunaliella* powder together with one or more activators of

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nuclear receptors versus a method of improving the method of treatment taught by the prior art comprising the administration of the instantly claimed ingredients.

Thus, at the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method for treating diabetes mellitus taught by Levy to provide the claimed method of treatment because Beck teaches that the oral administration of bezafibrate reduces the insulin level in normolipidaemic patients suffering from diabetes mellitus; Pan teaches that his method reduces or prevents the onset of diabetes mellitus and the onset of atherosclerosis in mammals, in Column 4, lines 27-34; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPAR γ agonist, *i.e.*, a thiazolidinedione, achieves synergistic action of the RXR/ PPAR γ heterodimers so as to enhance adipogenic and antidiabetic effects of PPAR γ ; and, Smith teaches that his method for treating diabetes mellitus comprising administering rosiglitazone provides a beneficial effect on glycaemic control, on page 1, lines 19-22. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed method because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*,

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47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, the claimed invention is no more than the combining of old and well-known ingredients used in well-known methods of treating the claim-designated disease conditions comprising the administration of the claim-designated ingredients.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 1 amended and Claims 8-10 is/are remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (U) and Levy et al. (W) in view of Pan et al. (B), Craig et al. (P) and Druzgala et al. (E), and further in view of Yoko et al. (V). Newly applied as necessitated by amendment.

The rejection stands for the reasons set forth in the previous Office action, the reasons set forth above, and for the reasons set forth below.

Applicant's arguments and the declaration of Aviv Shaish filed under Rule 132 have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

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where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the combined teachings of Levy (U) and Levy (W) were relied upon for the reasons set forth in the previous Office and for the reasons set forth above, and with particular to the teachings of Yoko as set forth above herein. Because the combined teachings of Levy (U and W) taught the claimed method for treating diabetes mellitus and atherosclerosis for the instantly claimed ingredients, as further evidenced by the teachings of Yoko as set forth above, the secondary references of Pan, Craig and Druzgala were relied upon because Pan taught a method of reducing the risk of or treating diabetes mellitus comprising administering an effective amount of an antihyperlipoproteinemic agent, e.g., fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate and clinofibrate, either alone or in combination with a cholesterol lowering drug, ACE inhibitor, and in Column 4, lines 27-34, Pan further taught that the ingredients of his invention prevent the onset of coronary artery disease and prevent the onset of atherosclerosis in mammalian species; Craig taught a method of treating diabetes mellitus and diabetes mellitus related disease conditions, e.g., atherosclerosis, comprising administering rosiglitazone; and, Druzgala taught methods of treating disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia, comprising the administration of a therapeutically effective amount of a thiazaolidinedione, i.e., troglitazone (for example, REZULIN), pioglitazone, and rosiglitazone.

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With regard to the declaration of Shaish filed under Rule 132, wherein Shaish provides experimental results showing that the combination of *Dunaliella* powder together with a PPAR γ (*i.e.*, rosiglitazone) shows an unexpected improvement in the treatment of diabetes as opposed to the results with either component alone, the Office deems that the Shaish' disclosure is not commensurate in scope to the limitations of the claimed invention as the claimed invention is directed to a method for treating diabetes mellitus comprising administering to a subject an effective amount of the claim-designated ingredient in together with one or more activators of nuclear receptors vs. a method for improving treating diabetes mellitus comprising administering to a subject an effective amount of crude *Dunaliella* powder together with one or more activators of nuclear receptors.

Thus, at the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method for treating diabetes mellitus and atherosclerosis taught by the combined teachings of Levy (U and W) to provide the claimed method of treatments because Pan teaches that his method reduces or prevents the onset of diabetes mellitus and the onset of atherosclerosis in mammals, in Column 4, lines 27-34; and, Craig and Druzgala teach that thiazolidinediones are suitable for the treatment diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed method because it is well known that its *prima facie* obvious to combine

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two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, the claimed invention is no more than the combining of old and well-known ingredients used in well-known methods of treating the claim-designated disease conditions comprising the administration of the claim-designated ingredients.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 1 as amended and Claims 2, 8-10 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoko et al. (X) in view of Levy et al. (U). Newly applied as necessitated by amendment.

The teachings of Yoko are set forth above. Yoko teaches the claim-designated methods except for wherein the powder is encapsulated. However, it would have been obvious to one of ordinary skill in the art to modify the method of disease treatment taught by Yoko by administering the reference powdered extract of *Dunaliella bardawil*

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in an encapsulated form to provide the claimed invention because at the time the invention was made it was known in the art of pharmacy that the oral administration of the claim-designated algal composition in an encapsulated form was conventional, as evidenced by the teachings of Levy set forth above. At the time the invention was made, one of ordinary skill in the would have been motivated and one would have a reasonable expectation of success to modify the method of treatment taught by Yoko by administering the reference powdered extract of *Dunaliella bardawil* in an encapsulated form to provide the claimed invention because Levy teaches that the oral administration of *Dunaliella bardawil* provides a mean of delivering the therapeutic algal composition. Thus, the claimed invention would have been merely a matter of judicial selection to one practicing the invention to pick and choose the form for the oral administration of the referenced algal compositions to effect a result variable for the treatment of the claim-designated disease conditions, since at the time the invention was made Yoko teaches that the oral administration of effective amounts of a powdered extract of *Dunaliella* had therapeutic effects for the claim-designated disease condition, and given that Levy teaches that the encapsulation of a powdered extract of the claim-designated algal extract has therapeutic beneficial effects.

According, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

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Claim 1 as amended and Claims 2-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoko et al. (V) and Levy et al. (U) in view of Beck (A), Criere et al. (O), Clark et al. (C) and Heyman et al. (D). Newly applied as necessitated by amendment.

The combined teachings of Yoko and Levy were set forth above. The combined teachings of Yoko and Levy teach the claimed invention except for the instantly claimed one or more activators of nuclear receptors. However, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Yoko and Levy to provide the claimed method of treatment because at the time the invention was made fibrates and thiazolidinediones were known in the art for their beneficial effect for treating the claim-designated disease conditions. Firstly, in Column 1, lines 11-16, Beck teaches that the administration of bezafibrate is widely used for the treatment of hyperlipidaemias (hypertriglyceridaemias and hypercholesterolaemias); Criere teaches a method of treating hyperlipemia, including hypercholesterolemia and hypertriglyceridemia, comprising the administration of an effective amount of fenofibrate; and Clark suggests that the administration of clofibrate, gemfibrozil, fenofibrate and bezafibrate reduce serum cholesterol. Secondly, Heyman teaches a method of treating hypertriglyceridemia comprising administering an effective amount of a thiazolidinedione, e.g., troglitazone, BRL 49653, pioglitazone, ciglitazone, WAY-120,744, englitazone, AD 5075, and darglitazone, in combination with an RXR agonist to a subject. At the time the invention was made, one of ordinary skill

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in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the methods for reducing triglycerides and/or increasing HDL cholesterol levels in the plasma of subject taught by the combined teachings of Yoko and Levy to provide the claimed method of treatment because Criere, Beck and Clark teach that the claim-designated fibrates are effective in lowering serum cholesterol; and, in Column, 2, lines 5-11, Heyman teaches that the combination of an RXR agonist and a PPAR γ agonist, *i.e.*, a thiazolidinedione, achieves synergistic action of the RXR/ PPAR γ heterodimers so as to enhance adipogenic and antidiabetic effects of PPAR γ . Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed method because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, the claimed invention is no more than the combining of old and well-known ingredients used in well-known methods of treating the claim-designated disease conditions comprising the administration of the claim-designated ingredients.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed


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invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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